Adjunctive intra-arterial mechanical thrombectomy versus medical care alone for ischemic stroke – a systematic review and meta-analysis

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4-5
INTRODUCTION			
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Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7-8
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Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-11

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11-12
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Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13-14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-20
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FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

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Title

Adjunctive intra-arterial mechanical thrombectomy versus medical care alone for ischemic stroke: a systematic review and meta-analysis

Registration

The protocol of this systematic review was registered in Prospective Register of Systematic Reviews (PROSPERO 2015:CRD42015019340).

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Word count

Abstract: 286 words

Main Text: 3277 words

References: 49

Figures: 12 (4 in text; 8 supplementary)

Tables: 4

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Abstract

Background: Early reperfusion with thrombolysis improves survival and functional outcomes among ischemic stroke patients. Uncertainty exists whether adjunctive intra-arterial mechanical thrombectomy (AIMT) helps further improve outcomes.

Objectives: To evaluate the efficacy and safety of AIMT in ischemic stroke patients.

Data sources: MEDLINE, CENTRAL, Web of Science, SciELO and LILACS from inception to April 2015. Reference lists were crosschecked.

Study eligibility criteria, participants and intervention: All ischemic stroke randomized controlled trials (RCTs) comparing AIMT with medical care alone, no language or time restrictions.

Data extraction: Two independent reviewers.

Study appraisal and synthesis methods: Cochrane risk of bias assessment tool was applied. Random-effects meta-analysis was performed to estimate pooled risk ratio (RR) and 95% confidence intervals (95%CI).

Findings: Pooled analysis from eight RCTs (n=2414) showed that AIMT is associated with an increased proportion of patients experiencing good (modified Rankin Scale [mRS]≤2) and excellent (mRS≤1) outcomes 90 days after stroke, without differences in mortality or symptomatic intracranial haemorrhage rates, compared with patients randomized to receive medical care alone. Results for the subgroup of studies published in 2015 (five RCTs; n=1278), which are more suited to test the true effect of AIMT on its index disease, yielded an RR of 1.73 (95%CI: 1.49 to 2.01) and 2.04 (95%CI 1.62 to 2.58) for achieving a good and excellent outcome, respectively, without heterogeneity among studies results.

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Limitations: All RCTs were open-label. Follow-up was limited to 90 days. Risk of bias was moderate across studies.

Conclusions and implications of key findings: There is moderate-to-high quality evidence that AIMT provides beneficial functional outcomes after ischemic stroke secondary to anterior large vessel occlusion, without increased detrimental effects when compared to medical care alone.

Funding for the systematic review: none.

Systematic review registration number: CRD42015019340

Keywords

Stroke, thrombectomy, meta-analysis

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Introduction

Ischemic stroke is the leading cause of death worldwide[1], its incidence is rising in individuals under 75 years old[2] and the global burden attributable to stroke is increasing.[3] Therefore, along with preventive measures, effective treatments are needed to reduce the deleterious consequences of stroke.

Arterial occlusion is the culprit of ischemic stroke. Lack of blood supply leads to functionally and radiologically distinct areas, namely the infarct core and the potentially salvageable ischemic penumbra.[4] The amount of viable tissue among the penumbra area is reduced over time. Consequently, early reversal of vascular occlusion limits the volume of damaged tissue and correlates with outcome.[5] By achieving timely reperfusion, thrombolysis improves survival and functional recovery.[6 7] However, the recanalization rates of medical care alone are not ideal[8] and the use of concomitant reperfusion techniques, such as adjunctive intra-arterial mechanical thrombectomy (AIMT), may reverse vessel occlusion more effectively and thus help further improve outcomes.

Results from published randomized controlled trials (RCTs) on AIMT are heterogeneous and uncertainty exists regarding its clinical benefit.[9-12] Therefore, we conducted a systematic review with meta-analysis to evaluate the efficacy and safety of AIMT versus medical care alone in adult patients with ischemic stroke.

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Methods

Protocol and guidance

The protocol followed PRIMA-P guidelines[13] and was registered at PROSPERO 2015 (registration number CRD42015019340; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019340). The methods of the systematic review followed PRISMA[14] guidelines. Reporting of statistical data followed SAMPL[15] guidelines.

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Eligibility criteria

RCTs reporting on the efficacy and safety of AIMT, independently of the chosen device, compared with medical care alone for ischemic stroke in adults (≥18 years old). Studies had to mention functional outcome and mortality at 90 days after symptom onset as trial endpoints. No study was dismissed due to poor quality, language, or time restrictions. Observational, non-controlled, or non-randomized interventional studies were excluded.

Information sources

Electronic identification of reports was conducted in MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, SciELO, and LILACS. Grey literature was searched via appropriate databases (i.e.: OpenGrey, Database of Abstracts of Reviews of Effects (DARE), British Library Thesis Service). Clinical trial registries were also consulted (i.e.: ClinicalTrials.gov, European Union Clinical

Trials Register, World Health Organization International Clinical Trials Registry Platform, ISRCTN Registry, Stroke Trials Registry). The last electronic search was on 23 April 2015.

The references of potentially eligible RCT were crosschecked.

Search strategy

The strategy combined the terms (cerebrovascular disorder OR stroke) with (mechanical thrombolysis OR embolectomy OR thrombectomy). The Cochrane Highly Sensitive Search Strategy was used to retrieve RCT.[16] See *Annexe S1* for an exemplified search strategy.

Study selection

Reports retrieved were screened for potential eligibility by title and abstract analysis. Afterwards, the full text was screened for appropriateness of inclusion. Two independent screeners (FBR, JBN) conducted this process. Disagreements were solved by consensus or by a third party (DC). The inter-observer bias was calculated as the percentage of agreement achieved.[17]

Data collection process

Two independent parties (FBR, JBN) extracted data from the included RCT to a standardised electronic form. Disagreements were solved by consensus or by a third party (DC). Gathered data was double-checked (JC).

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Outcomes and prioritization

The primary efficacy outcome was the proportion of patients achieving a good functional outcome at 90 days after symptom onset defined as a modified Rankin Scale (mRS)[18] score between 0 and 2 – that is, functional independency. The primary safety outcome was all-cause mortality at 90 days. The secondary efficacy outcome was the proportion of patients achieving an excellent functional outcome at 90 days (mRS≤1). The secondary safety outcome was the proportion of patients with symptomatic intracerebral haemorrhage (sICH) as defined in the SITS-MOST study.[8]

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Risk of bias in individual studies

Risk of bias of individual studies was independently assessed by two authors (FBR, JBN) using the Cochrane Collaboration Risk of Bias Tool.[16] Three additional criteria were sought: independent funding, trial stopped early, and clinical trial registration to assess whether the trial was retrospective or prospectively registered. The risk of bias was considered high if the trial was retrospectively registered due to uncertainty on how Rankin assessments were done and to the fact that some of the trial outcomes are subjective.

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Data synthesis

Random-effects meta-analyses (RevMan 5.3.3 software) weighted by the inverse-variance method were performed to estimate pooled risk ratio (RR) and 95% confidence interval (95%CI). Sample size and event rates were considered when using the Mantel-Haenszel method. RR was chosen as effect measure due to greater similarity of relative estimates between studies with different designs, populations and

lengths of follow-up.[19] Raw data was converted to RR. Heterogeneity was assessed with the Cochran Q test and the I^2 test.[20] When significant risk differences were found, we also determined absolute effects and derived the additional number of participants with events per 1000 that benefitted or suffered harm from receiving the studied intervention.

A secondary analysis of the primary efficacy outcome was performed in order to explore the risk of non-event: the risk of patients achieving an unfavourable functional outcome – dependency or death – at 90 days after symptom onset (mRS>2). The results were expected to be different of the inverse of the pooled analysis because, despite the same sample size, the weighting method for statistical analysis takes into account the differences in event rates.

Trial Sequential Analyses (TSA) were performed for primary outcomes using TSA version 0.9 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, 2011) to explore whether cumulative data were adequately powered to evaluate outcomes.[21] The required information size and the O'Brien-Fleming adjacent trial sequential alpha spending monitoring boundaries were calculated based on a two-sided 5% risk of a type I error, 20% risk of a type II error (power of 80%), risk reduction based on pooled analysis, the weighted incidence of events in the control group, and heterogeneity. Power of the primary outcomes findings was interpreted if significance was reached with either a minimum sample size, or crossing trial sequential alpha spending monitoring boundary.

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Due to inequalities in trial design, including patient populations and interventions,[22] (see results section), data for all outcomes were presented a priori separately according to the year of publication of the trial. Further subgroup analysis was planned for: gender; trials with different risk of bias; thrombectomy devices (including only trials that used a single device); time to treatment; rt-PA administration; and stroke characteristics.

Meta-biases

Publication bias was assessed through visual inspection of funnel plots' asymmetry if more than ten studies per outcome were available[16]. Egger's[23] and Peters' tests[24] were performed.

Confidence in cumulative evidence

Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology.[25]

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in [recruitment, or] the design and implementation of the study. There are no plans to involve patients in dissemination

Results

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Study selection

Electronic searches yielded 329 records after deduplication. The inter-observer agreement between screeners was good, as quantified by a Cohen's kappa coefficient of 0.70 (95%CI 0.50 to 0.89).[17] Eight studies were included: IMS III[26], SYNTHESIS Expansion[27], MR RESCUE[28], MR CLEAN[29], ESCAPE[30], EXTEND-IA[31], SWIFT-PRIME[32], and REVASCAT[33] (Figure 1). Published protocols and supplementary material of these studies were consulted whenever needed.[34-41]

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Study characteristics

All studies were multicentre, parallel, prospective randomised open blinded endpoint (PROBE) clinical trials (Table 1). All but three – SYNTHESIS, MR CLEAN and REVASCAT - were international. The number of participants ranged from 70 to 656. Altogether, the studies involved 2414 participants, 1312 in the AIMT arm and 1102 in the medical care arm, either based in an intention to treat (ITT) or in a modified-ITT population.

The main inclusion criteria entailed adult stroke patients with time from symptom onset to AIMT between 5 and 12 hours. Most studies required a time from symptom onset to thrombolysis of 4.5 hours. MR RESCUE, MR CLEAN, ESCAPE, and REVASCAT accepted patients not illegible for thrombolysis. The follow-up period was 90 days in all trials.

The overall baseline characteristics of included patients were similar between arms across studies (Table 2). Mean age ranged from 61 to 71 and gender distribution was

approximately 1:1 in all studies. Stroke severity ranged from 13 to 20 points in the National Institute of Health Stroke Scale (NIHSS). All studies focused on anterior circulation strokes, but IMS II and SYNTHESIS also allowed posterior circulation strokes. ESCAPE, MR CLEAN, REVASCAT, and SWIFT-PRIME included only proximal artery strokes. All studies required radiological confirmation of large vessel occlusion as an inclusion criterion except IMS III and SYNTHESIS. For patient inclusion, perfusion imaging depicting potentially salvageable brain tissue was only required in EXTEND-IA and SWIFT-PRIME studies.

The intervention evaluated was AIMT ± intravenous rt-PA. The control arm received medical care, in most studies including intravenous rt-PA (Table 3). IMS III, SYNTHESIS, MR RESCUE, and MR CLEAN accepted other intra-arterial interventions in the AIMT arm (intra-arterial rt-PA and urokinase-type plasminogen activator). Compliance with thrombectomy in the intervention arm ranged from 30.9% to 95.1% and with rt-PA in the control arm ranged from 28.1% to 100%.

Selected devices varied among studies. IMS III, MR RESCUE, SYNTHESIS and ESCAPE allowed multiple devices (i.e. Merci retriever, Penumbra system, Solitaire FR, and Trevo), while EXTEND-IA, REVASCAT, and SWIFT-PRIME opted for Solitaire FR, and MR CLEAN for Merci retriever. The time from stroke ictus to endovascular treatment ranged from 225 to 355 minutes.

Risk of bias within studies

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The overall risk of bias was moderate among studies (Figure 2). Random sequence generation, blinding of outcome assessment, and selective reporting were considered as low risk items across studies. Outcome assessment at 90 days was conducted in person on ESCAPE, EXTEND-IA, and SWIFT-PRIME, in person or through video visualisation on REVASCAT, and by telephone on SYNTHESIS and MR CLEAN. IMS III and MR RESCUE did not report the method used for outcome assessment evaluation. Allocation concealment and blinding of participants and personnel were classified as high risk due to study design. Additionally, all studies but SYNTHESIS were industry sponsored, five were stopped early, either due to efficacy or futility, and one (MR RESCUE) was retrospectively registered. Concerning attrition bias, IMS III and MR CLEAN showed imbalances between withdrawals in the active and control arms and in MR RESCUE and REVASCAT the reduced number of participants limited considerations.

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Synthesis of results

All studies reported the sought outcomes. Results of individual studies were incorporated in forest plots (Figures 3, 4, S1, S2 and S3).

Overall, 911 out of 2014 patients (45.2%) reached a good functional outcome at 90 days. AIMT-treated patients had a higher chance of achieving a good outcome (RR 1.39; 95% CI: 1.11 to 1.75; Figure 3) with an increase of 124 (95% CI: 35 to 239) patients attaining a good outcome per each 1000 additional AIMT-treated patients compared with medical care alone. Conversely, the RR for not achieving a good functional outcome (mRS>2) was 0.82 (95% CI: 0.72 to 0.95; Figure S1.

Considerable statistical heterogeneity (I^2=76%, p=0.0001) was present for overall pooled studies results, but not for pooled results of studies published in 2013 (I^2=0%; p=0.62) and in 2015 (I^2=0%; p=0.97). Furthermore, efficacy outcome results were significantly different (p<0.0001) between these two subgroups of trials. No differences were found in the proportion of patients reaching a mRS≤2 (Figure 3) or a mRS≤1 (Figure S2 among 2013 trials results. In contrast, pooled RR for 2015 trials was 1.73 (95% CI: 1.49 to 2.01), representing an increase of 192 (95%CI: 129 to 266) patients attaining a good outcome (mRS≤2) per each 1000 additional AIMT-treated patients compared with medical care alone. Additionally, pooled RR for mRS≤1 (Figure S2 was 2.04 (95% CI: 1.62 to 2.58; I^2=0, p=0.99), representing an increase of 132 (95% CI: 79 to 201) patients attaining an excellent outcome per each 1000 additional AIMT-treated patients compared with medical care alone. Sensitivity analysis excluding trials with either low compliance with rt-PA in the control arm (MR RESCUE) or trials with low (<40%) thrombectomy compliance (IMS III and SYNTHESIS) yielded similar results for all efficacy outcomes as all these trials happened to be published in 2013.

All-cause mortality at 90 days was captured in 415 out of 2387 participants (17.4%), without differences between arms (RR 0.91; 95% CI: 0.77 to 1.09; I^2= 0%, p=0.45; Figure 4). Furthermore, no differences existed between results from trials published in 2013 and in 2015 (p=0.54).

Overall, 119 out of 2418 patients (4.9%) experienced sICH, without differences between treatment groups (RR 1.07; 95% CI: 0.74 to 1.53; I^2=0%, p=0.84; Figure S3.

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Furthermore, no differences existed between results from trials published in 2013 and in 2015 (p=0.96).

Additional analysis

The number of included studies limited the evaluation of publication bias with funnel plots. Egger's (p=0.333) and Peters' (p=0.318) tests were not suggestive of publication bias or small studies' effects.

Regarding TSA analysis, the proportion of patients with unfavourable outcome (mRS>2) was 66% and a RR reduction (RRR) of 18% was assumed based on the RR of 0.82 estimated for the dependency outcome. The cumulative evidence reached 41.9% of minimum information size required (5766 patients) adjusted for the obtained RRR and heterogeneity (Figure S4). The cumulative evidence was not adequately powered for mortality evaluation, reaching 15.5% of the required information size for a 9% RRR of mortality (Figure S5).

Predetermined subgroup analysis based on gender (Figure S6), rt-PA administration across all patients (rt-PA versus no rt-PA; Figure S7), and thrombectomy device (Solitaire FR versus Merci retriever; Figure S8) showed similar results to the findings obtained from main pooled analysis for the primary efficacy outcome (p=0.61, p=0.34, p=0.85, respectively). Subgroup analysis according to risk of bias, stroke characteristics, and time to treatment were not performed due to similarity of risk of bias across studies, lack of robust data for posterior circulation strokes, and for time to AIMT.

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Discussion

Summary of evidence

The main finding of this systematic review is that there is moderate-to-high quality evidence indicating that AIMT improves the probability of an ischemic stroke patient being functionally independent at 90 days after stroke comparing to medical care alone, without increased mortality or sICH (Table 4).

These conclusions are based on eight RCTs enrolling 2414 ischemic stroke patients. Although pooled analysis of these eight RCTs yielded statistical significant and clinical relevant results, significant heterogeneity was found among studies results. This heterogeneity was driven by differences in methodological and clinical features between studies, which enabled us to separate the eight RCTs into two subgroups of trials: the first, comprised of 2013 publications – including the IMS III, SYNTHESIS, and MR RESCUE trials –, and the second, comprised of 2015 publications – encompassing the MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, and REVASCAT trials.

As far as inclusion criteria are concerned, large vessel occlusion – the index problem amenable by thrombectomy – was not required for enrolment in IMS III and SYNTHESIS. Also, in SYNTHESIS the cause of stroke was different in both arms, with a higher rate of atrial fibrillation in the control arm and of artery dissection in the treatment arm. Regarding the intervention arm, in IMS III patients were given a lower than recommended dose of IV rt-PA and in SYNTHESIS IV rt-PA was withheld. In

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MR RESCUE a low rate of administration of IV rt-PA was observed in both arms. Compliance with thrombectomy in the intervention arm was low (<40%) in IMS III and SYNTHESIS. Finally, the use of currently outdated first generation devices lead to suboptimal revascularization rates in IMS III and MR RESCUE, and, at least in IMS III, may have contributed to substandard groin puncture to reperfusion times.[42]

Large vessel occlusion was an obligatory enrolment criterion in all 2015 studies – either diagnosed by CT angiography or by MR angiography. In these trials both study arms received the recommended dose of IV rt-PA if there were no contraindications. Compliancy rates with thrombectomy in the intervention arm were high (>77%) and the majority of 2015 studies used Solitaire FR, a newer generation device that appears to have higher recanalization rates and reduced deployment times when compared with previous devices.[43]

The focus on large vessel occlusion scenarios, the use of two simultaneous reperfusion techniques – IV rt-PA and thrombectomy – and more efficient devices are probably pivotal factors that help explain the difference between the statistical significant and clinical relevant results observed among 2015 RCTs but not among 2013 RCTs. It is therefore without surprise that previous systematic reviews and meta-analysis, focusing mainly in 2013 publications[9, 10, 12], have failed to detect treatment differences. Considering the pathophysiology of ischemic stroke and the knowledge acquired from IMS III[44], SYNTHESIS[45], as well as from previous rt-PA trials[7], it can be drawn that faster, more efficient recanalization is of paramount importance to reduce the infarction of penumbral brain tissue and thus contribute to improved clinical outcomes.

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To sum up, due to the above-mentioned reasons as well as due to the rate and dosage of IV rt-PA usage in both studies arms, the studies published in 2015 are more suited to test the true effect of AIMT on its index disease. We therefore consider that pooled results from these studies evaluate more accurately the benefit of adjunctive thrombectomy after IV rt-PA in ischemic stroke caused by large vessel occlusion. Based on these results, we conclude that patients undergoing AIMT are twice more likely to be without disability and 1.5 times more likely to be functionally independent, both 90 days after an ischemic stroke caused by large vessel occlusion.

Weaknesses of the study

Despite gathering data from multicentric RCTs, the information included was not powered enough to relate the clinical effects to AIMT. Furthermore, observational studies may be more adequate than RCTs to evaluate safety, as these may include patients that are usually excluded from RCTs and the follow-up is frequently longer. Lastly the magnitude of effects may have been exaggerated by a stricter patient selection, and a higher level of study site selection and interventionist proficiency comparing with the real world.

The PROBE design of all studies has greater similarities with everyday clinical practice and is more cost-effective than double-blinded RCT.[46] Nonetheless, PROBE studies eliminate placebo effect, a phenomenon not discarded in blind sham-controlled trials, and are more likely to lead to researcher and patient biases[46] and to patient drop-out after randomization.

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In stroke trials it is customary to provide outcomes at 90 days.[47] However, spontaneous neurological recovery usually ceases only after six months[47], so longer follow-ups could have more accurately predicted the endpoints.

Finally, another limitation was the overall moderate risk of bias – all trials had PROBE design, most were industry funded, five were stopped early, and one had retrospective registration. Nevertheless, previous reports noted that industry-sponsored studies can accurately report outcomes[48] and that in truncated trials for efficacy treatment effects may not be substantially larger than for completed trials.[49]

Implications for clinical practice

Recommending AIMT as standard of care in ischemic stroke caused by large vessel occlusion will require restructuring of comprehensive stroke centres and of interventional neuroradiologists training in order to enhance the available resources.

Due to the baseline characteristics of the included population, the pooled clinical benefit attributable to AIMT may only be applicable to patients younger than 85 years old with large vessel anterior circulation strokes and if the intervention is performed within 6 to 8 hours from ictus. Of note, adding thrombectomy to standard IV rt-PA opens the conventional treatment window from 4.5 hours to at least 6 hours in ischemic stroke due to large vessel occlusion.

Implications for research

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Future studies should evaluate the optimal timeframe for AIMT, its benefit in patients who have contraindications for thrombolysis, in posterior circulation strokes and in older populations, and its safety profile. Also, longer follow-ups should be provided.

Conclusion

In contrast to previous publications[9 10 12] and results obtained in initial trials, this systematic review and meta-analysis shows that AIMT provides beneficial functional outcomes after ischemic stroke secondary to anterior large vessel occlusion, without increased detrimental effects when compared to medical care alone.

Cost-effectiveness analysis should be pursued before widespread implementation of AIMT and restructuration of comprehensive stroke centres.

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Section 1: What is already known on this subject

Intravenous thrombolysis is the standard therapy for acute ischemic stroke but recanalization rates are not ideal. The use of concomitant reperfusion techniques, such as adjunctive intra-arterial mechanical thrombectomy (AIMT), may help to further improve clinical outcomes.

Section 2: What this study adds

This systematic review and meta-analysis of 8 randomised controlled trials provide moderate quality evidence indicating that AIMT, when provided up to 6 to 8 hours after anterior circulation large vessel ischemic stroke, leads to improved functional

outcomes at 90 days without increased mortality or symptomatic intracerebral haemorrhage.

This evidence supports the need to restructure current neurointerventional resources and to change current clinical practice.

Contributions

JJF and JC were the guarantors. All authors contributed to the drafting of the manuscript, the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. FBR developed the search strategy. FBR and JBN conducted the report screening, study inclusion, data extraction, and result interpretation and discussion. DC performed the statistical analysis, and conducted result interpretation and discussion. JJF and JC provided expertise on stroke and on methodology. All authors read, provided feedback and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) No author has support for the submitted work; (2) JJF have speaker and consultant relationships with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme that might have an interest in the submitted work in the previous 3 years; (3)

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their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) FBR, JBN, DC and JC have no non-financial interests that may be relevant to the submitted work.

Sources of funding for the study and declaration of independence from funders

No financial or non-financial support of any kind was provided. There is no dependency relation between researchers and funders or sponsors.

Data sharing

No additional data available.

Ethics approval

No required.

Transparency declaration

The lead authors (JC and JJF) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figures

Figure 1 – Study selection flow diagram

Figure 2 – Risk of bias summary

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Figure 3 – Forest plot for a good outcome (mRS≤2) at 90 days, including year of study publication subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.

Figure 4 – Forest plot for mortality at 90 days, including year of study publication subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.

Tables

Trial	Source	Trial period	Location	No. of centres	No. of patients*	Primary outcome	Enrolment criteria			
							Age, y	Symptom onset to		NIHSS
								rt-PA, h	AIMT, h	
IMS III[26]	Broderick et al., 2013	2006 - 2012	USA, CAN, AUS, ESP, DEU, FRA, NLD	58	656	mRS ≤ 2 at 90d	18 - 82	3	5	≥ 10***
SYNTHESIS[27]	Ciccone et al., 2013	2008 - 2012	ITA	24	362	mRS ≤ 1 at 90d	18 - 80	4.5	6	≤ 25
MR RESCUE[28]	Kidwell et al., 2013	2004 - 2011	USA, CAN	22	127	mRS scores at 90d	18 - 85	4.5**	8	6 - 29
MR CLEAN[29]	Berkhemer et al., 2015	2010 - 2014	NLD	16	502	mRS scores at 90d	≥18	4.5**	6	≥ 2
ESCAPE[30]	Goyal et al., 2015	2013 - 2014	CAN, USA, KOR, IRL, GBR	22	316	Median mRS at 90d	≥18	4.5**	12	Unrestricted
EXTEND-IA[31]	Campbell et al., 2015	2012 - 2014	AUS, NZL	10	70	Reperfusion at 24h and NIHSS at 3d	≥18	4.5	6	Unrestricted
SWIFT PRIME[32]	Saver et al., 2015	2012 - 2015	USA, FRA, DEU, ESP, CHE, DNK, AUT	39	196	mRS scores at 90d	18 - 80	4.5	6	8 - 29

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REVASCAT[33]	Jovin et al., 2015	2012 - 2014	ESP	4	207	mRS scores at 90d	18 - 85	4.5**	8	≥ 6

Table 1 - Characteristics of included studies. y, years; rt-PA, recombinant tissue plasminogen activator; h, hours; AIMT, adjuvant intra-arterial mechanical thrombolysis; NIHSS, National Institute of Health Stroke Scale; USA, United States of America; CAN, Canada; AUS, Australia; ESP, Spain; DEU, Germany; FRA, FRANCE; NLD, Netherlands; mRS, modified Rankin Scale; d, days; ITA, Italy; KOR, South Korea; IRL, Ireland; GBR, United Kingdom; NZL, New Zealand; CHE, Switzerland; DNK, Denmark; AUT, Austria. * Intention to treat population; ** If illegible; *** ≥8 if CT or MR angiographic evidence of internal carotid artery, first division of middle cerebral artery (M1) or basilar artery occlusion.

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Trial	AIMT arm					Medical care arm				
	Intervention	n*	Age, y mean ± SD	Male, no. (%)	NIHSS, mean ± SD	Intervention	n*	Age, y mean ± SD	Male, no. (%)	NIHSS, mean ± SD
IMS III[26]	IV rt-PA ± IV heparin ± thrombectomy and/or IA rt-PA	434	63 ± 11.07	218 (50.2)	20 ± 5.54	IV rt-PA	222	61 ± 10.23	122 (55.0)	18 ± 3.69
SYNTHESIS[27]	IV heparin ± thrombectomy and/or IA rt-PA	181	66 ± 11	106 (59)	13 ± 5.98	IV rt-PA	181	67 ± 11	103 (57)	13 ± 6.73
MR RESCUE[28]	Thrombectomy ± IA rt-PA ± IV heparin ± IV rt-PA	70/64***	64 ± 12.78***	30 (46.9)***	17 ± 4.72***	± IV rt-PA	57/54***	67 ± 16.48***	27 (50)***	17 ± 5.73***
MR CLEAN[29]	± IV rt-PA + thrombectomy ± IA rt-PA or IA uPA	233	65 ± 16.04	135 (57.9)	17 ± 5.22	± IV rt-PA	267	66 ± 15.58	157 (58.8)	18 ± 5.96
ESCAPE[30]	Thrombectomy ± IV rt-PA	165	71 ± 15.71	79 (47.9)	16 ± 5.24	± IV rt-PA	150	70 ± 15.72	71 (47.3)	16 ± 5.99
EXTEND-IA[31]	IV rt-PA ± thrombectomy	35	69 ± 12.3	17 (49)	17 ± 5.41	IV rt-PA	35	70 ± 11.8	17 (49)	14 ± 7.73
SWIFT PRIME[32]	IV rt-PA ± thrombectomy	98***	65 ± 12.5***	54 (55.1)***	17 ± 5.27***	IV rt-PA	93***	66 ± 11.3***	45 (48.4)***	16 ± 4.52***
REVASCAT[33]	Thrombectomy ± IV rt-PA	103	66 ± 11.3	55 (53.4)	17 ± 4.51	± IV rt-PA	103	67 ± 9.5	54 (52.4)	16 ± 5.26

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Table 2 - Characteristics of included patients. AIMT, adjuvant intra-arterial mechanical thrombolysis; NIHSS, National Institute of Health Stroke Scale; IV, intravenous; rt-PA, recombinant tissue plasminogen activator; IA, intra-arterial; uPA, urokinase-type plasminogen activator. * Intention to treat population; ** Per protocol population; *** Modified intention to treat population.

Trial	AIMT arm					Medical care arm	
	n*	Thrombectomy no. (%)	IV rt-PA no. (%)	IA rt-PA no. (%)	Thrombectomy + IV rt-PA no. (%)	n*	IV rt-PA no. (%)
IMS III[26]	434	170 (39.2)	434 (100)**	266 (61.3)	170 (39.2)	222	222 (100)
SYNTHESIS[27]	181	56 (30.9)	0 (0)	109 (60.2)	0 (0) / 56 (30.9)***	181	178 (98.3)
MR RESCUE[28]	70	61 (87.1)	28 (40.0)	8 (11.4)	28 (40.0)	57	16 (28.1)
MR CLEAN[29]	233	195 (83.7)	203 (87.1)	25 (10.7)	N/S	267	242 (90.6)
ESCAPE[30]	165	151 (91.5)	120 (72.7)	N/A	120 (72.7)	150	118 (78.7)
EXTEND-IA[31]	35	27 (77.1)	35 (100)	N/A	27 (77.1)	35	35 (100)
SWIFT PRIME[32]	98****	87 (88.8) ****	98 (100) ****	N/A	87 (88.8) ****	93****	93 (100) ****
REVASCAT[33]	103	98 (95.1)	70 (68.0)	1 (1.0)	N/S	103	80 (77.7)

Table 3 - Characteristics of the intervention within treatment arms. AIMT, Adjuvant intra-arterial mechanical thrombolysis; IV, intravenous; IA, Intra-arterial; rt-PA, recombinant tissue plasminogen activator; N/S, Not specified; N/A, Not applicable. * Intention to treat population; ** Approximately two thirds of the standard dose *** Intra-arterial rt-PA; **** Modified intention to treat population

Table 4 – Summary of findings table

Adjunctive intra-arterial mechanical thrombectomy (AIMT) compared to medical care alone for ischemic stroke

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with medical care alone	Risk difference with Adjunctive intra-arterial mechanical thrombectomy (AIMT)
mRS≤2 90d (independency outcome)	2414 (8 RCTs)	□□□◯ MODERATE [1]	**RR 1.39** (1.11 to 1.75)	Study population	
				319 per 1000	**124 more per 1000** (35 more to 239 more)
mRS≤2 90d (independency outcome) - year of publication subgroup analysis - 2015	1278 (5 RCTs)	□□□◯ MODERATE [1]	**RR 1.73** (1.49 to 2.01)	Study population	
				264 per 1000	**192 more per 1000** (129 more to 266 more)
Mortality 90d	2387 (8 RCTs)	□□□◯ MODERATE [1]	**RR 0.91** (0.77 to 1.09)	Study population	
				180 per 1000	**16 fewer per 1000** (41 fewer to 16 more)
mRS≤1 90d (excellent outcome)	2414 (8 RCTs)	□□□◯ MODERATE [1]	**RR 1.52** (1.12 to 2.05)	Study population	
				191 per 1000	**99 more per 1000** (23 more to 200 more)
mRS≤1 90d (excellent outcome) - year of publication subgroup analysis - 2015	1278 (5 RCTs)	□□□□ HIGH [1]	**RR 2.04** (1.62 to 2.58)	Study population	
				127 per 1000	**132 more per 1000** (79 more to 201 more)
Symptomatic intracerebral haemorrhage	2418 (8 RCTs)	□□◯◯ LOW [1,2]	**RR 1.07** (0.74 to 1.53)	Study population	
				48 per 1000	**3 more per 1000** (12 fewer to 25 more)

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***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

GRADE: Grading of Recommendations Assessment, Development and Evaluation working group; CI: Confidence interval; RR: Risk ratio; AIMT: Adjunctive intra-arterial mechanical thrombectomy; mRS: modified Rankin Scale; RCT: Randomized controlled trial, d: day

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect**; Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different**; Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effec**; Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. The overall risk of bias was moderate among included studies.
2. Confidence interval fails to exclude important benefit or important harm

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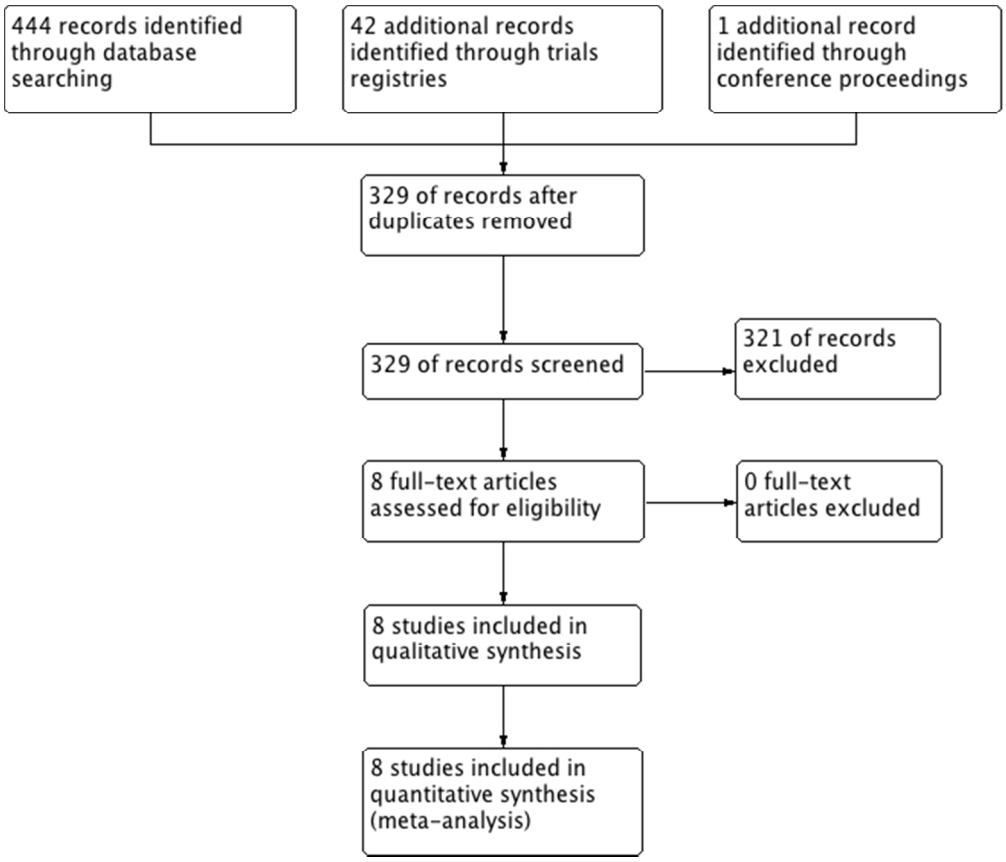

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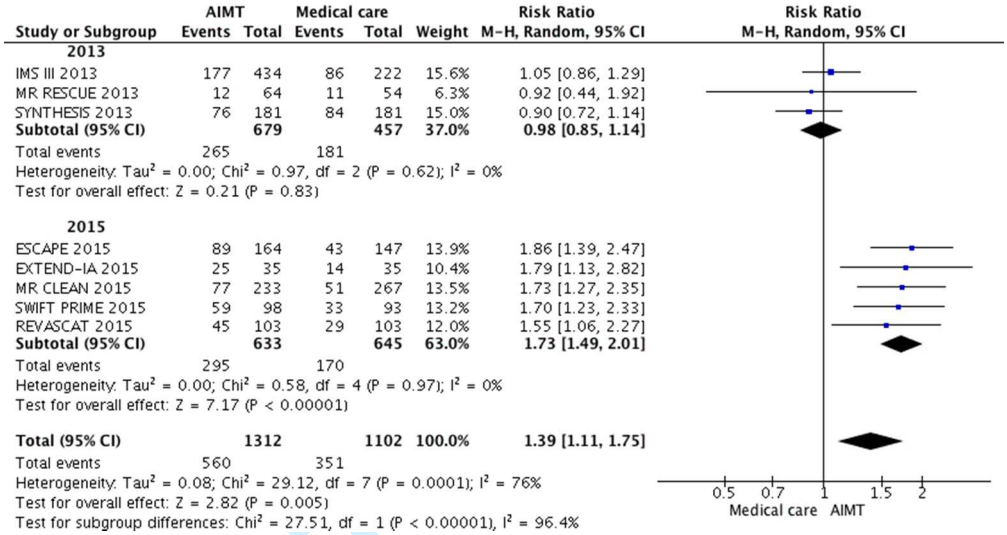
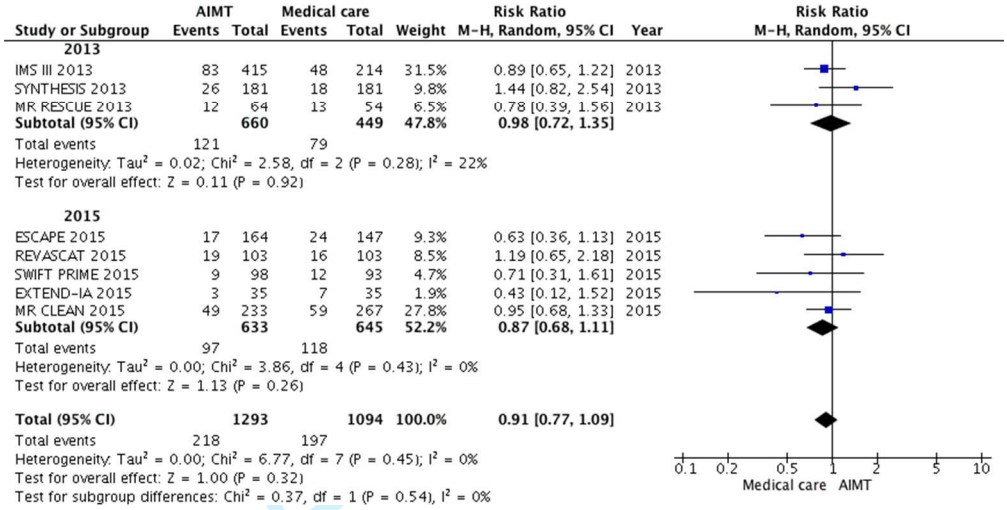




Supplementary material

Annexe S1 - Exemplified search strategy for MEDLINE (OvidSP)

1 exp cerebrovascular disorders/

2 exp basal ganglia cerebrovascular disease/

3 exp brain ischemia/

4 exp carotid artery diseases/

5 exp carotid artery thrombosis/

6 exp intracranial arterial diseases/

7 exp cerebral arterial diseases/

8 exp stroke/

9 (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.

10 ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.

11 or/1-10

12 exp mechanical thrombolysis/

13 exp embolectomy/

14 exp thrombectomy/

15 (mechanical adj3 (thrombectom* or thromboembolectom* or thrombo-embolectom* or thrombolys* or remov* or disrupt* or clot* or embolectom* or recanalis* or recanaliz* or retriev*)).tw.

16 neurothrombectom*.tw.

17 merci.tw.

18 penumbra system.tw.

19 solitaire.tw.

20 trevo.tw.

21 or/12-20

22 randomized controlled trial.pt.

23 controlled clinical trial.pt.

24 randomized.ab.

25 placebo.ab.

26 clinical trials as topic.sh.

27 randomly.ab.

28 trial.ti.

29 or/22-28

30 and/11,21,29

31 exp animals/ not humans.sh.

32 30 not 31

Figure S1 - Forest plot for a non-favourable functional outcome (mRS>2) at 90 days, including year of study publication subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.

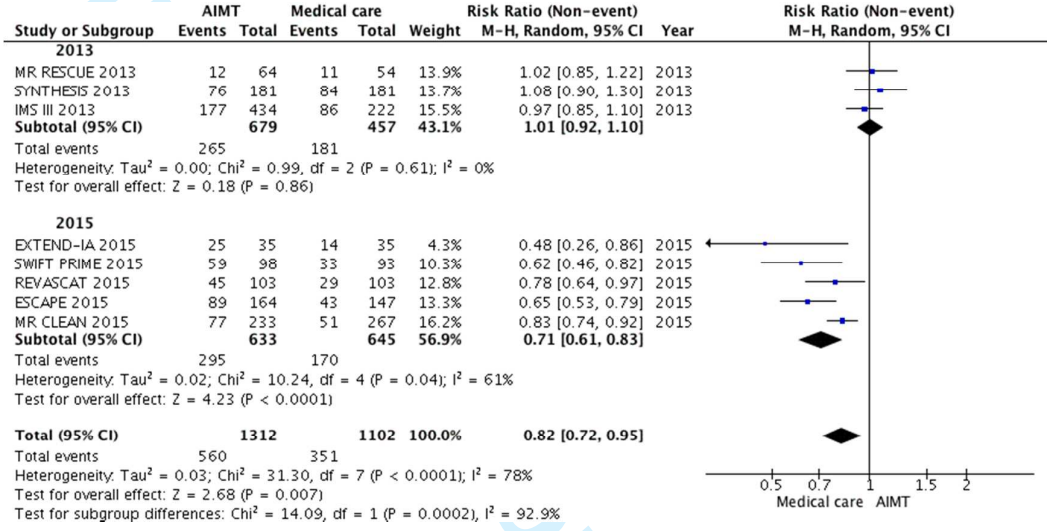


Figure S2 - Forest plot for an excellent outcome (mRS≤1) at 90 days, including year of study publication subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.

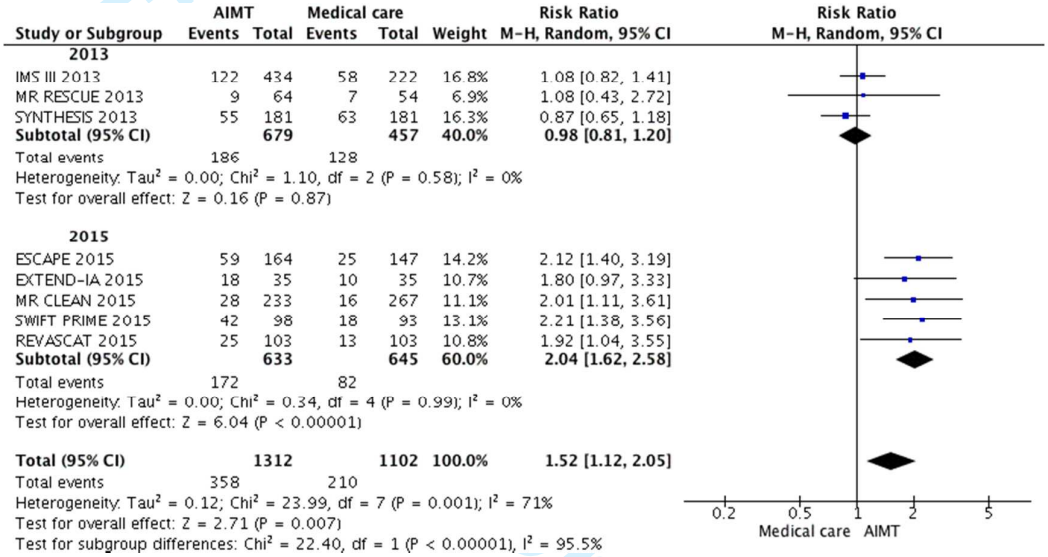
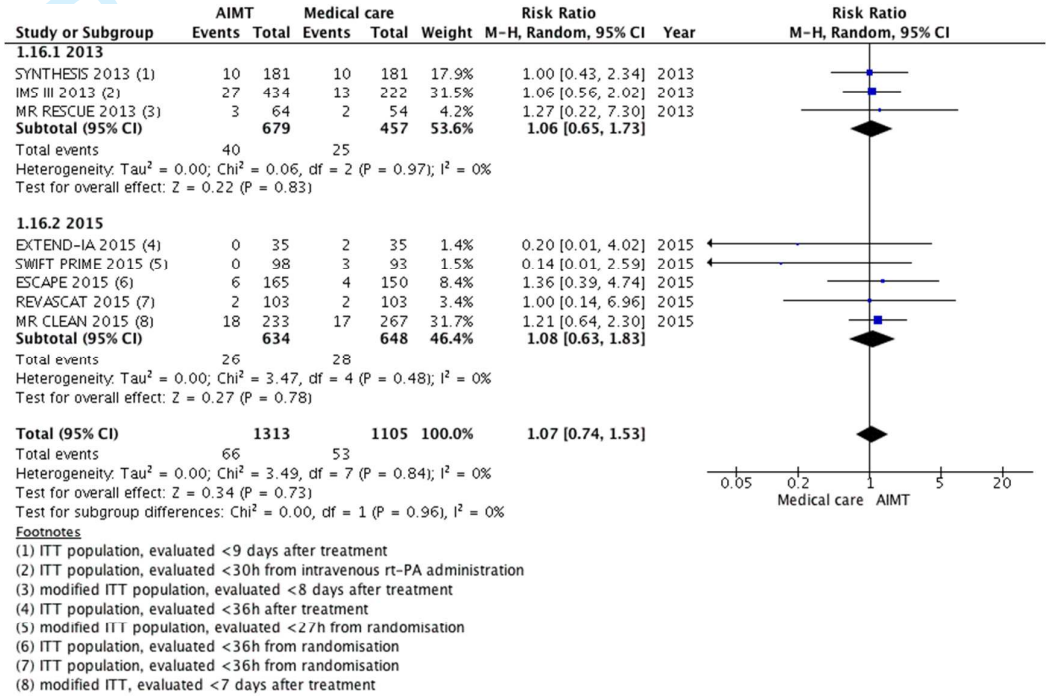


Figure S3 - Forest plot for symptomatic intracerebral haemorrhage, including year of study publication subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.



Footnotes
(1) ITT population, evaluated <9 days after treatment
(2) ITT population, evaluated <30h from intravenous rt-PA administration
(3) modified ITT population, evaluated <8 days after treatment
(4) ITT population, evaluated <36h after treatment
(5) modified ITT population, evaluated <27h from randomisation
(6) ITT population, evaluated <36h from randomisation
(7) ITT population, evaluated <36h from randomisation
(8) modified ITT, evaluated <7 days after treatment

Figure S4 – Trial sequential analysis for the primary efficacy outcome.

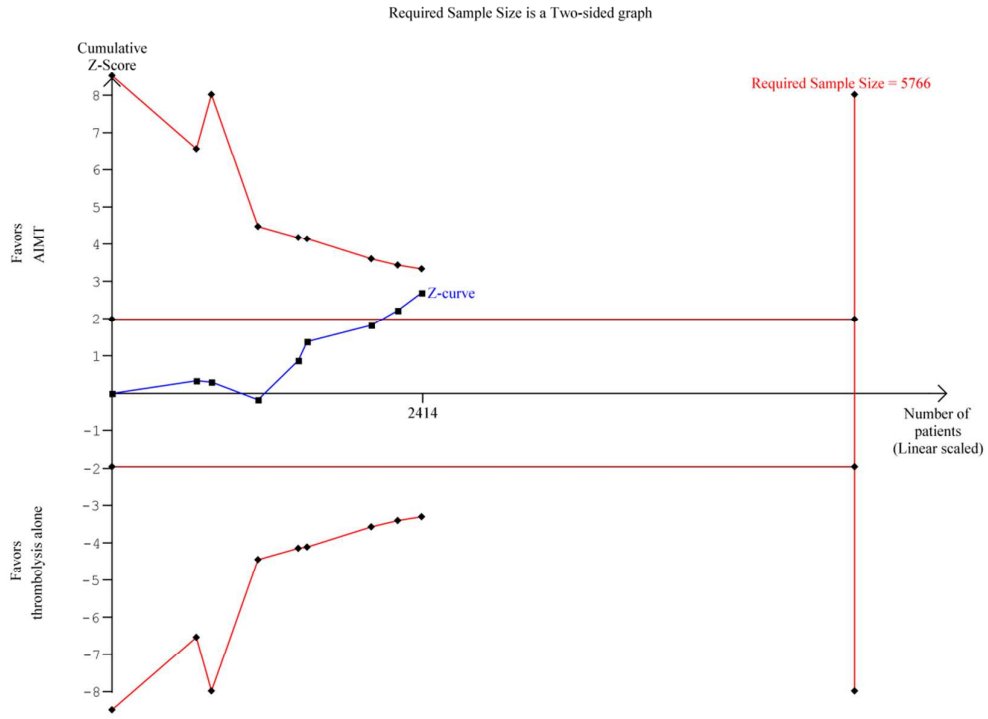


Figure S5 - Trial sequential analysis for the primary safety outcome.

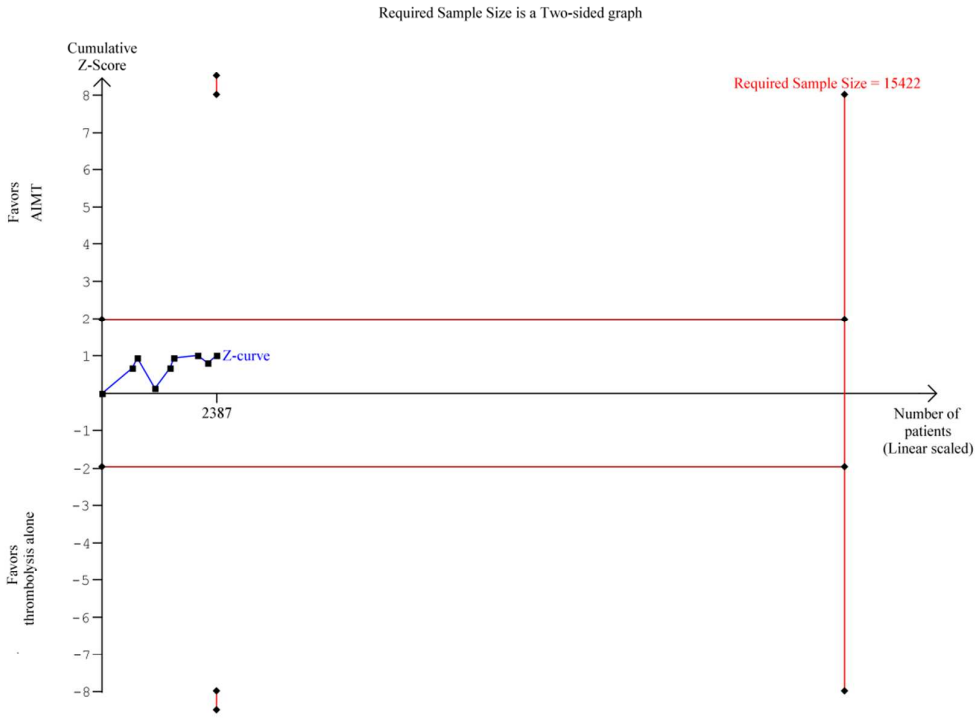


Figure S6 – Forest plot for a good outcome (mRS≤2) at 90 days, including gender subgroup analysis. SE, Standard error; IV, Inverse variance method; CI, Confidence interval; AIMT, Adjuvant intra-arterial mechanical thrombectomy.

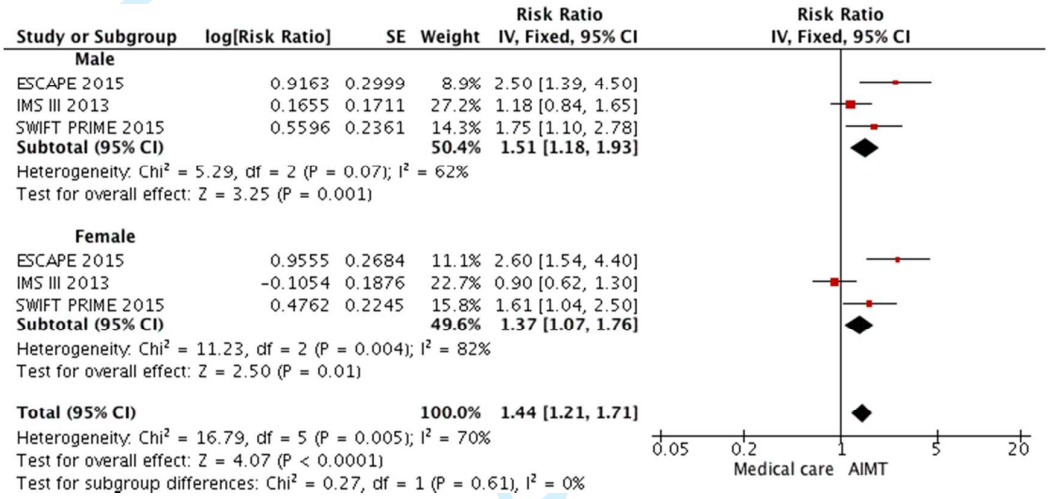


Figure S7 – Forest plot for a good outcome (mRS≤2) at 90 days, including rt-PA administration subgroup analysis. SE, Standard error; IV, Inverse variance method; CI, Confidence interval; AIMT, Adjuvant intra-arterial mechanical thrombectomy.

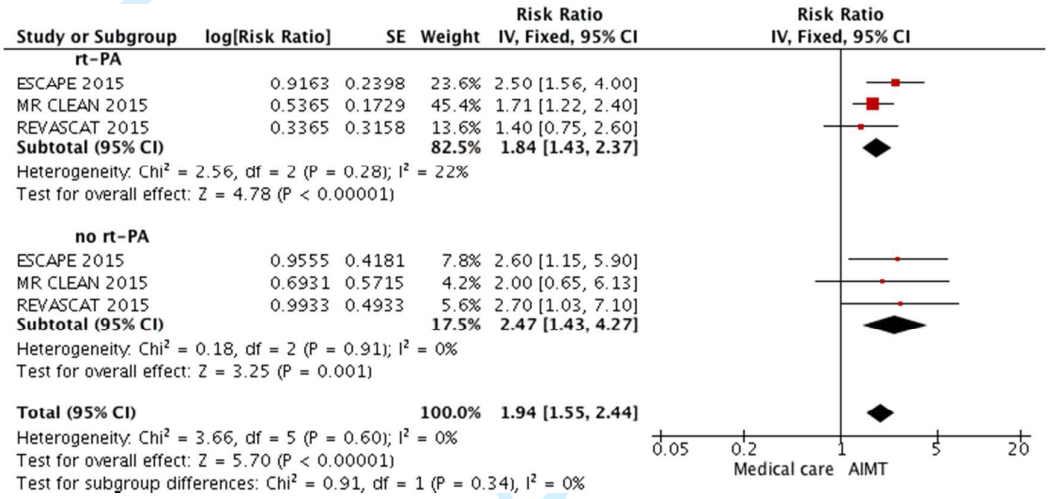


Figure S8 – Forest plot for a good outcome (mRS≤2) at 90 days, including thrombectomy device subgroup analysis. AIMT, Adjuvant intra-arterial mechanical thrombectomy; M-H, Mantel-Haenszel method; CI, Confidence interval.